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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/729,043	12/04/2000	M. Suzanne Bradshaw	4167-4000	4527

7590 12/17/2002

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/729,043	BRADSHAW ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-20* is/are pending in the application.

4a) Of the above claim(s) *14-17 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 19* is/are rejected.

7)☒ Claim(s) *18,19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 14-20 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group II in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the claims of Group II recite the use of the DNA of Group I, hence a search of both groups is not an undue burden.

This is not found persuasive because the inventions of Group I and II are patentably distinct for the reasons set forth of the record mailed on 8/27/02. The DNA of Group I is not limited to the use of Group II. Therefore, a search of both groups is not co-extensive. As such, to examine both groups in a single application is burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 14-17 and 20 are withdrawn from consideration for being directed to non-elected subject matter. Claims 18 and 19 are currently under examination.

Claim Objections

Claims 18 and 19 are objected to as being dependent upon a non-elected base claim (15). But for the purpose of examination, the limitations of claim 15 will be read into claims 18 and 19. Applicant is advised to rewrite the claim in independent form including all of the limitations of the base claim (15).

Claim Rejections - 35 USC § 101

Claims 18 and 19 are rejected under 35 U.S.C. 101 because they are not directed to statutory subject matter. It is PTO policy not to issue claims that encompass humans (see 1077

OG 24, April 21, 1987). This rejection may be overcome by inserting "non-human" before "mammals" or "embryos."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

The nature of the invention is a method of cloning, manipulating and performing mutagenesis of defined segment of DNA having flanking sequences using site-specific targeting, and subsequently generating knock-in or knock-out mammal.

The breadth of claim is very broad. In the instant case, the claims encompasses a method of cloning, manipulation of any segment DNA and making any type of knock-in or knock-out non-human mammal, and transgenic embryo by using said DNA generated by the recited cloning method.

The amount of guidance and working example in the specification is limited. The specification does not provide any method steps for making such knock-in or knockout animals and transgenic embryos. The claims do not include any active method steps for making a transgenic mammal or a transgenic embryo. Further, the specification does not provide an enabling disclosure to make a knock-in or knock-out mammal except a knockout or knock-in mouse. The specification only teaches production of knock-in or knock-out mouse by homologous recombination in embryonic stem cells (ES). The specification fails to teach the generation of any other types of knock-in or knock-out mammal. Without teaching from the specification, one skilled in the art would have to turn to prior art for guidance to make and use the transgenic mammal as claimed.

The state of art at the time of filing only teaches the generation of knock-in or knock-out mouse by homologous recombination. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell must be available to carry out the method. To date, there is no teaching from the art that homologous recombination in a somatic cell and subsequent introduction of said cell to a blastocyst would generate an offspring carrying gene mutation. The specification does not teach such a method either. The only species in which the ES cell is available is the mouse (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-

like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p.65). Likewise, Mullins et al. (1996, Clin. Invest. Vol 97, no. 7, 1557-1560) teach that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p.1558, column 2, paragraph 1). Therefore, no knockout mammals can be made for any species other than the mouse at the time of filing. As such, the invention is enabled for a knock-in or knockout mouse, generated by using ES cells.

In view of the limited guidance in the specification and the prior art, one skilled in the art would have to engage in undue experimentation to practice the claimed method.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a method of cloning, manipulating and performing mutagenesis of defined segment of DNA. However, the recitation of "further comprising the step of using the defined segment of DNA create knock-in or knockout strains of mammals/transgenic embryos" renders the claims indefinite because it is unclear what kind of the method the claims encompass. In addition, it is unclear whether the final product is the "defined segment of DNA" or "knock-

in knockout mammals/transgenic embryos." The recitations of "strains of mammals" and "embryos" also render the claims indefinite because it is unclear how many mammals and embryos the claims encompass. It is suggested to use singular terms.

Claims 18 and 19 provide for the use of "defined segment of DNA," but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 18 and 19 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-Marie Falk

ANNE-MARIE BAKER
PATENT EXAMINER

Celine Qian, Ph.D.
December 15, 2002